REMARKS

Claims 1-3, 11, 21, 43-46, 54, 71, 86-87, 107-108 and new claims 110-133 are currently pending. New claims 110-133 are supported by the specification and do not contain new matter.[1]

I. 35 U.S.C. 112, First Paragraph Rejection

Reconsideration is requested of the rejection of claims 1-3, 11, 21, 43-46, 54, 71, 86-87, and 107-108 under 35 U.S.C. 112, first paragraph. The claims have been amended to cancel the term "preventing." In view of this amendment, the rejection is moot and may properly be withdrawn.

II. 35 U.S.C. §103(a) Rejection

Reconsideration is requested of the rejection of claims 1-3, 11, 21, 43-46, 54, 71, 86-87, and 107-108 under 35 U.S.C. §103(a) in view of U.S. Patent No. 5,672,583 ('583 Patent), U.S. Patent No. 5,629,343 ('343 Patent), WO 97/20824, WO 97/48685, Barni et al.[2], and Muller-Bohn et al.[3]

Claim 1 is directed to a method to treat a neoplasia disorder in a mammal. The method comprises administering to the mammal the matrix metalloproteinase inhibitor

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[1]Claims 110-127 are supported by the specification at pages 9-10. Claims 128-133 are supported by the specification at pages 136 and 142 for topotecan and at pages 142 and 221-222 for irinotecan.

[2]Barni et al., (1998) Tumori 84(1):45-47, abstract only.

[3]Muller-Bohn et al., (1997) Deutsche Apotheker Zeitung 137(41):54-55. This article is in German. Applicants have had the abstract and summary translated to English, a copy of which is enclosed with this response for the Office's convenience. As such, Applicants' remarks set-forth in this response are based upon the portion of the article that has been translated to English. If the Office has a copy of the entire article that has been translated to English, applicants request a copy be provided to them.

N-hydroxy-2,2-dimethyl-4-[[4-(4-pyridinyloxy)phenyl]sulfonyl]3-thiomorpholinecarboxamide and an antineoplastic agent selected from irinotecan, topotecan and a combination thereof.

The '583 patent discloses a class of carboxy-peptidyl compounds that are described as "useful inhibitors of matrix metalloendoproteinase-mediated diseases " including "tumor invasion in certain cancers."[4] According to the '583 patent, the disclosed compounds may also be co-administered with "a PMN elastase inhibitor."[5] But nowhere does the reference disclose or suggest a combination of N-hydroxy-2,2-dimethyl-4-[[4-(4-pyridinyloxy)phenyl]sulfonyl]3-thiomorpholinecarboxamide and one or more **antineoplastic agents** selected from the group consisting of **irinotecan and topotecan** for use in the treatment of a neoplasia disorder, as required by claim 1. Moreover, '583 patent does not even disclose a matrix metalloproteinase inhibitor having the structure of the matrix metalloproteinase inhibitor recited in claim 1 (*i.e*, N-hydroxy-2,2-dimethyl-4-[[4-(4-pyridinyloxy)phenyl]sulfonyl]3-thiomorpholinecarboxamide).

The '343 patent discloses a class of N-(mercaptoacyl)peptidyl compounds that are described as "useful inhibitors of matrix metalloendoproteinases."[6] According to the '343 patent, the disclosed compounds may be employed to treat "degenerative diseases" such as "arthritis, periodontal disease, and corneal ulceration" and "certain cancers."[7] This patent also reports that the disclosed compounds may be co-administered with "a PMN elastase inhibitor."[8] Nowhere, however, is it disclosed or

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[4]U.S. Patent No. 5,672,583, abstract.

[5]Id., column 21, lines 37-40.

[6]U.S. Patent No. 5,629,343, abstract.

[7]Id., abstract and column 5, lines 64-67.

[8]Id., abstract and column 8, lines 55-57.

suggested to administer a combination of N-hydroxy-2,2-dimethyl-4-[[4-(4-pyridinyloxy)phenyl]sulfonyl]3-thiomorpholinecarboxamide and an **antineoplastic agent** selected from the group consisting of **irinotecan and topotecan** for use in the treatment of a neoplasia disorder, as required by claim 1. In addition, the '583 patent fails to even disclose a matrix metalloproteinase inhibitor having the structure of the matrix metalloproteinase inhibitor recited in claim 1 (i.e, N-hydroxy-2,2-dimethyl-4-[[4-(4-pyridinyloxy)phenyl]sulfonyl]3-thiomorpholinecarboxamide).

WO 97/20824 discloses a class of compounds that are described as being matrix metalloproteinase inhibitors.[9] In particular, the reference is directed to a process for making the disclosed compounds. WO/972024 does not disclose or suggest combining the matrix metalloproteinase inhibitor recited in claim 1 with irinotecan or topotecan, **or any** other compound for that matter, for use in the treatment of a neoplasia disorder.

WO 97/48685 discloses a class of diketopiperazine compounds that are described as inhibitors of matrix metalloproteinases. The diketopidperazine compounds disclosed in WO 97/488685 have vastly different formulas than the matrix metalloproteinase recited in claim 1. Moreover, while the reference reports that the diketopiperazine compounds may be used "optionally in combination with current chemotherapy and/or radiation,"[10] it fails to identify a single chemotherapeutic agent or even a single class of chemotherapeutic agents that may be used in the proposed combination therapy. Thus, this disclosure is so vague and general as to be non-informative.

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[9]WO 97/20824, abstract.

[10]WO 97/48685, page 28, lines 31-32.

Barni et al. disclose that the aromatase inhibitor anastrolzole "has no inhibitory effect on prolactin secretion in metastatic breast cancer."[11] Anastrolzole is not a compound recited in claim 1. Moreover, Barni et al. do not disclose matrix metalloproteinase inhibitors in combination with either irinotecan or topotecan for use in the treatment of a neoplasia disorder, as required by claim 1.

Muller-Bohn et al. disclose that irinotecan and topotecan belong to a class of topoisomerase inhibitors. They fail, however, to disclose matrix metalloproteinase inhibitors in combination with either irinotecan or topotecan for use in the treatment of a neoplasia disorder, as required by claim 1.

In the absence of any disclosure of the combination employed in the method of claim 1, a *prima facie* case for obviousness is lacking.

The Office asserts that it would have been obvious to combine two compositions (i.e., N-hydroxy-2,2-dimethyl-4-[[4-(4-pyridinyloxy)phenyl]sulfonyl]3-thiomorpholinecarboxamide and irinotecan or topotecan), each of which is disclosed in the prior art to be useful for same purpose, in order to form a third composition that is used for the very same purpose (i.e., treatment of neoplasia).[12] But the cited art, taken singly or together, provide no basis for this conclusion.

Among the many compounds and classes of compounds the '583 patent, '343 patent, WO 97/20824, WO 97/48685, Barni et al., and Muller-Bohn et al. propose, none offer any guidance that would have motivated a skilled artisan to prepare the combination employed in claim 1. The '583 patent, the '343 patent, WO 97/20824, and WO 97/48685 each disclose classes of matrix metalloproteinase inhibitors that are distinguishable from the matrix metalloproteinase inhibitor required by claim 1. Further, the '343 patent merely suggests co-administering N-(mercaptoacyl)peptidyl compounds

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[11]Barni et al., (1998) Tumori 84(1):45-47, of which only the abstract was cited in Paper 23. As such, Applicants' comments detailed above regarding the disclosure of Barni et al. only reflect review of the abstract.

[12]Paper 23 at page 7.

with "a PMN elastase inhibitor." Irinotecan and topotecan are not "PMN elastase inhibitors" and the '343 patent fails to suggest co-administering N-(mercaptoacyl)peptidyl compounds with irinotecan and topotecan or any other compound of their class for any purpose. While WO 97/488685 reports that certain diketopiperazine compounds may be used "optionally in combination with current chemotherapy and/or radiation", no further guidance is provided which would have motivated a person of ordinary skill to select the compounds required by claim 1 of the rather large universe of chemotherapeutic agents; furthermore, WO 97/48865 fails to disclose or suggest even a single agent that would be suitable to combine with a matrix metalloproteinase inhibitor.

Even more revealing, not one of the cited references discloses or suggests combining a matrix metalloproteinase inhibitor with either irinotecan or topotecan for use in the treatment of a neoplasia disorder, as recited in claim 1. Barni et al. fail to disclose any compound recited in claim 1. And, although Muller-Bohn et al. disclose irinotecan and topotecan are topoisomerase inhibitors, they do not disclose or suggest combining either of these compounds with a matrix metalloproteinase inhibitor. Accordingly, a skilled artisan empowered with the cited art cannot fairly be deemed to be motivated to select N-hydroxy-2,2-dimethyl-4-[[4-(4-pyridinyloxy)phenyl]sulfonyl]3-thiomorpholinecarboxamide and combine it with either irinotecan or topotecan disclosed in Muller-Bohn et al. to form a composition for use in treating a neoplasia disorder, as required by claim 1. As stated in MPEP 2143, where there is no motivation to modify a reference as proposed, the proposed modification is not obvious.

In support of its position, the Office cites *In re Kerkhoven*.[13] *Kerkhoven*, however, is distinguishable. In *Kerkhoven*, the issue was whether the claimed process for the production of particulate detergent compositions containing a mixture of anionic and nonionic active detergent materials was patentable. The CCPA held that it was not

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[13]626 F.2d 848, 205 USPQ 1069 (CCPA 1980).

and, in so deciding, stated "[i]t is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, **in order to form a third composition** which is to be used for the very same purpose."[14] In contrast, claim 1 is directed to a method for treating a neoplasia disorder in a mammal and not merely a method of making a third composition. Furthermore, matrix metalloproteinase inhibitors interact with one or more metabolic pathways in a manner which is separate and distinct from that of either irinotecan or topotecan; thus, unlike in *Kerkhoven* it cannot be concluded that the use, in combination, has *the very same purpose* since the combination is being used for the purpose of interacting in metabolic pathway(s) in a manner which is distinguishable from the matrix metalloproteinase inhibitor, alone, or irinotecan or topotecan, alone. Notably absent from the art cited by the Office is any information from which it may be concluded that such multiple interactions would be beneficial; thus, unlike the situation in *Kerkhoven*, a person of ordinary skill would not have been motivated by the art cited by the Office to use the pharmaceutical agents required by claim 1, in combination.

In *Vaeck*, the Federal Circuit held that "both the suggestion and the reasonable expectation of success must be founded in the prior art, not the applicant's disclosure."[15] Without a reasonable expectation that the combination of the two separate compounds recited in claim 1 (i.e. the matrix metalloproteinase inhibitor and irinotecan or topotecan) would produce a composition that showed the physiological effect of treating neoplasia, the second prong of the test laid out in *Vaeck* has not been met.

Further, the Office has provided no reason or rationale as to why a skilled artisan would be motivated to combine the disclosure of **six separate** references: the '583 patent, the '343 patent, WO 97/20824, WO 97/48685, Barni et al., and Muller-Bohn et

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[14]626 F.2d at 850, 205 USPQ at 1072 (CCPA 1980), emphasis added.

[15]In re Vaeck, 947 F.2d 488, 493 (Fed. Cir. 1991).

al. For example, the Office has not provided any basis for concluding that it have been obvious for a skilled artisan to use the matrix metalloproteinase inhibitors disclosed in any of the '583 patent, the '343 patent, WO 97/20824, and WO 97/48685 in combination with irinotecan or topotecan which is disclosed by Muller-Bohn et al. for another purpose. The Office merely delineates bare assertions regarding what each reference purportedly discloses and then concludes that claim 1 is obvious. To properly establish a *prima facie* case of obviousness, the law requires more than conclusions supported by bare assertions.

For the foregoing reasons, the Office has failed to establish that claim 1 is *prima facie* obvious in view of the '583 patent, the '343 patent, WO 97/20824, WO 97/48685, Barni et al., and Muller-Bohn et al. Claims 2, 3, 11, 21, 43, 107, 108 and new claims 110-118 depend from claim 1, and are likewise patentable over these references for the reasons stated with respect to claim 1 and by reason of the additional requirements they introduce.

Claim 87 is also not obvious in view of the cited art. The composition of claim 87 comprises the same components as the composition employed in the method of claim 1. For all of the reasons detailed with respect to claim 1, therefore, the composition of claim 87 is patentable in view of the '583 patent, the '343 patent, WO 97/20824, WO 97/48685, Barni et al., and Muller-Bohn et al. New claims 132 and 133 depend from claim 87, and are likewise patentable over these references for the reasons stated with respect to claim 87 and by reason of the additional requirements they introduce.

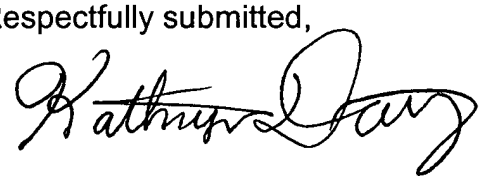
Amended claim 44 is directed to a method to treat a neoplasia disorder in a mammal. The method comprises administering to the mammal **radiation** and a combination of the matrix metalloproteinase inhibitor N-hydroxy-2,2-dimethyl-4-[[4-(4-pyridinyloxy)phenyl]sulfonyl]3-thiomorpholinecarboxamide and one or more antineoplastic agents selected from the group consisting of irinotecan and topotecan. Claim 44, therefore, involves administering the same composition to the mammal as does the method of claim 1, but also includes the step of administering **radiation**. For

all of the reasons detailed with respect to claim 1, claim 44 is not obvious in view of the cited art. In addition, nowhere does the cited art disclose administering radiation along with a composition comprising N-hydroxy-2,2-dimethyl-4-[[4-(4-pyridinyloxy)phenyl]sulfonyl]3-thiomorpholinecarboxamide and irinotecan or topotecan, as required by the method of claim 44. Claims 45, 46, 71, 86 and new claims 119-127 depend from claim 44, and are likewise patentable over these references for the reasons stated with respect to claim 44 and by reason of the additional requirements they introduce.

III. Conclusion

In light of the foregoing, Applicants request entry of the claim amendments, withdrawal of the claim rejections, and solicit an allowance of the claims. The examiner is invited to contact the undersigned attorney should any issues remain unresolved.

Respectfully submitted,



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